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EXAMINER

STRZELECKA, TERESA E

ART UNIT PAPER NUMBER

1637

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/876,375

Applicant(s)

WILLIAMS ET AL.

Examiner

Teresa E Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 16-28 and 55-59 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 18-28 is/are allowed.
- 6) ☒ Claim(s) 1, 5, 6, 10, 11, 13, 55, 57 and 59 is/are rejected.
- 7) ☒ Claim(s) 2-4, 7-9, 12, 14, 16, 17, 56 and 58 is/are objected to.
- 8) ☒ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed January 14, 2004. Claims 1-14, 16-28 and 55-60 were previously pending. Applicants amended claims 1 and 58, and cancelled claim 60. Claims 1-14, 16-28 and 55-59 are pending and will be examined.
2. Applicants' amendments, claim cancellations and arguments obviated the following rejections: rejection of claims 1-14, 16, 17, 58 and 60 under 35 U.S.C. 112, second paragraph; rejection of claim 60 under 35 U.S.C. 102 (b) over Hyman.
3. The provisional double patenting rejection of claims 1-14 and 16-28 over claims 22-36 of the co-pending application No. 09/876,374 is withdrawn in view of Applicants' cancellation of claims 22-36 in the 09/876,374 application.
4. The remaining rejections are maintained for reasons given in the "Response to Arguments" section below.

Response to Arguments

5. Applicant's arguments filed January 14, 2004 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 1, 5, 6, 10, 11, 13, 55, 57 and 59 over Hyman, Applicants argue the following:

a) Applicants teach applying an energy field to the sample, and separating the phosphate detectable moiety from the sample comprising an intact NP probe, whereas Hyman teaches using a column, and luciferase detection, where the presence of NTPs would interfere with quantitation. Applicants further argue that Hyman does not teach or suggest applying an energy field to the sample to separate the phosphate detectable moiety from the sample comprising an intact NP probe, since when Hyman applies the pressure, there is no intact NP probe present.

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b) Hyman does not teach a plurality of NP probes necessary to sequence the target nucleic acid, or a time sequence of the production of phosphate detectable moieties.

A general comment: according to Applicants' own definition, an intact NP probe with a phosphate detectable moiety can be a dNTP, where the intact NP probe is a dNMP, which is added onto a primer in the polymerization reaction, and the phosphate detectable moiety is a PPi, which is released by the polymerase. Therefore, Hyman teaches incorporation of an intact NP probe and production of the phosphate detectable moiety, PPi. Further, Applicants own definition of energy field is either an electric field or a pressure field (page 5, lines 17 and 18).

Regarding a), Hyman teaches sequencing of target DNA by pumping dNTPs through a column containing primer-DNA polymerase complex (see page 423, 424). The dNTP is incorporated by the polymerase, resulting in a production of PPi, which is removed with the flowing solution onto a next column. Therefore, since the dNMP (= intact NP probe) is now incorporated into the primer, it stays bound to the column, and PPi is separated from it by the flow (= pressure field). Therefore, Hyman teaches these two limitations.

Regarding b), Hyman teaches all four dNTPs necessary to sequence a target nucleic acid (page 423). Further, Hyman teaches time sequence of the production of the PPis (Fig. 8).

Therefore, Hyman teaches the limitations of claim 55.

The rejection is maintained.

Claim interpretation

6. Before proceeding with the rejection, Applicants' definition of a charge-switch NP probe is provided:

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“The term "charge-switch nucleotide" as used herein refers to a labeled nucleotide phosphate (e.g., .gamma.-NP-Dye) that upon release or cleavage of a phosphate detectable moiety (e.g., PPi-Dye) has a different net charge associated with the cleavage product compared to the intact nucleotide phosphate probe (e.g., .gamma.-NP-Dye).” (page 7, lines 28-31).

“The phrase "phosphate detectable moiety" refers to a detectable cleavage product from a NP probe of the present invention. Examples include, but are not limited to, PPi-Dye, PP-F, P-Dye, a phosphate fluorophore moiety, a terminal phosphate fluorophore moiety, a detectable moiety, charged groups, electrically active groups, detectable groups, reporter groups, combinations thereof, and the like.” (page 8, lines 6-10).

7. Applicants define energy fields as electric fields or pressure fields (page 5, lines 17 and 18).
8. The phrase “polymerase is immobilized in single molecule configuration” is interpreted as multiple polymerase molecules, each of which is immobilized on a solid support.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 5, 6, 10, 11, 13, 55, 57 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyman (Anal. Bioch., vol. 174, pp. 423-436, 1988; cited in the IDS and in the previous office action).

Regarding claim 1, Hyman teaches a method for sequencing DNA, the method comprising:

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a) providing a sample comprising an intact NP probe with a detectable moiety attached thereto, whereupon an enzymatic cleavage of said intact NP probe to incorporate said NP probe on a primer strand hybridized to a target nucleic acid, a phosphate detectable moiety is produced, wherein said phosphate detectable moiety carries a molecular charge which is different than the molecular charge which is different than the molecular charge of said intact NP probe (Hyman teaches providing a solution comprising one of four dNTPs (= intact NP probes) and pumping such solution through a column containing immobilized template-primer-DNA polymerase complex. Upon incorporation of a correct dNTP into a primer strand Ppi (=a phosphate detectable moiety) is produced. Hyman does not specifically teach that the phosphate detectable moiety carries a molecular charge which is different from the molecular charge of the intact dNTP, but since a nucleotide triphosphate has a net charge of -3 , after cleavage of two negative charges of PPi, the Ppi has a charge of -2 , which is different from the charge of intact dNTP (page 423, second and third paragraphs, Fig. 1).); and

b) applying an energy field to said sample, thereby separating said phosphate detectable moiety from said intact NP probe (Hyman teaches applying a flow pressure field to the column to separate the PPi from the template-primer-DNA polymerase complex, where the dNMP has been incorporated (page 425, 8th paragraph).

Regarding claim 5, Hyman teaches incorporation of dNTPs into a primer strand hybridized to a target nucleic acid using a DNA polymerase and release of PPi (page 423, second paragraph).

Regarding claim 6, Hyman teaches immobilized DNA polymerase (page 423, third paragraph).

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Regarding claim 10, Hyman does not specifically teach that the charge of PPi is greater than the charge of the intact NP probe, but since the intact dNTP has a charge of -3 and PPi has a charge of -2 , the charge of PPi is greater than a charge of intact NP probe.

Regarding claim 11, Hyman does not specifically teach that the charge of PPi is less than the charge of the intact NP probe, but since the intact dNTP has a charge of -3 and PPi has a charge of -2 , in terms of absolute values the charge of PPi is less than a charge of intact NP probe.

Regarding claim 13, Hyman teaches detection of PPi (page 424, first paragraph; Fig. 1).

Regarding claim 55, Hyman teaches a method of sequencing a nucleic acid (DNA), by providing a target nucleic acid, a polymerase priming moiety (= primer) a polymerase (=DNA polymerase) and a plurality of intact NP probes (= dNTPs) (page 423, first and second paragraphs),

mixing the target nucleic acid, primer, polymerase and dNTPs under conditions permitting target dependent polymerization of plurality of dNTPs under conditions capable of providing a time sequence of a plurality of phosphate detectable moieties (page 423, second paragraph; Fig. 1; page 426, 4th paragraph; Fig. 8); and

detecting over time plurality of phosphate detectable moieties to provide a sequence of target nucleic acid (Fig. 8).

Regarding claim 57, Hyman teaches PPis (pyrophosphates) (page 423, second paragraph).

Regarding claim 59, Hyman teaches DNA polymerase immobilized on DEAE-Sepharose beads (page 423, third paragraph; page 425, second paragraph).

Allowable Subject Matter

11. No references were found teaching or suggesting claims 2-4, 7-9, 12, 14, 16-28, 56 and 58. Claims 18-28 are allowed.

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12. Claims 2-4, 7-9, 12, 14, 16, 17, 56 and 58 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
March 23, 2004



JEFFREY FREDMAN
PRIMARY EXAMINER